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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/061,979 | 01/31/2002 | Jeremy S. Lee | 080129-000100US | 2049 |

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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/061,979 | LEE ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-14 and 17-22* is/are pending in the application.

4a) Of the above claim(s) *5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-14 and 18-22* is/are rejected.

7)☒ Claim(s) *4 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to an amendment filed 6/2/05. Claims 2, 3, 15 and 16 are cancelled. Clams 1, 4, 14 and 17 have been amended. Claim 5 has been withdrawn. Claim 1, 4 and 6-22 are under examination in this office action.

### *Response to Amendment*

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were necessitated by applicants' amendment and therefore, this action is final.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-14 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing antibodies in response to M-DNA, does not reasonably provide enablement for a method of eliciting an immune response to an antigen encoded by the M-DNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method of eliciting an immune response using metal containing nucleic acid comprising two strands of nucleic acid, which are joined by hydrogen bonds and interchelated with divalent metal cations or M-DNA. M-DNA has the properties of electrical conductance as well as being nuclease resistant. Therefore, introduction of the nuclease resistant M-DNA can result in prolonged response *in vivo*. The invention utilizes a combination of molecular biology and clinical techniques.

2) **Scope of the invention.** The only actual use of eliciting an immune response as recited in the instant claims is for immunization or a therapeutic immune response. While applicants have provided guidance for the production of antibodies in animals using M-DNA in the specification and in a Declaration filed 9/14/04, applicants have not provided an enabling disclosure for eliciting an immune response. The specification lacks guidance for the induction of therapeutic immune responses.

3) **Number of working examples and guidance**. The specification teaches construction of metal containing nucleic acids in which divalent metal cations such as $Ni^{2+}$, $Co^{2+}$ and $Mg^{2+}$ are interchelated with the hydrogen bonded base pairs and coordinated to a nitrogen atom of the

aromatic bases. The metal containing nucleic acid has the property of electrical conductance by accepting electrons from an electron donor. M-DNA is proposed to be useful in detection systems for the identification of PCR products, ligation reactions, for the detection of particular genomic sequences and to monitor presence of nucleic acid binding moieties in a sample.

Furthermore, M-DNA is nuclease resistant and therefore applicants propose its use in M-DNA to mediate physiological response *in vivo* such as to generate an immune response. Applicants demonstrate that the M-DNA is immunogenic by injecting $Ni^{2+}$ containing M-DNA intraperitoneally into Balb/C mice. Mice immunized with M-DNA show antibody titres to M-DNA. The disclosure neither provides examples of using M-DNA to express antigenic protein nor teaches that the DNA specifically disclosed in example 1 and used in examples 2-4 would transcribe normally.

In a Declaration filed 9/14/04, applicants demonstrate that tgD DNA encoded by M-DNA can be expressed. Furthermore, introduction of the M-DNA into mice resulted in an increase in tgD-specific IgG titre as determined by an ELISA. However, applicants do not demonstrate that an immune response, which entails much more than antibody production, is elicited.

4) **State of Art**. DNA vaccines are sought after to develop immune responses that protect against diseases. Falo et al teach (Falo et al pages 1239-1240) that "Since the first observation that the simple injection of plasmid DNA vectors result in the induction of an antibody response, many preclinical studies have suggested that DNA-based immunization can induce protective and therapeutic immune responses against infectious and neoplastic diseases". The immune responses are described as including a myriad of responses of which one response is the production of antibodies (see e.g. Rekvig, page 1, col 2 and figure 1). However, the success to

date of a DNA vaccine to elicit an immune response has been limited (see e.g. Aidsmap, paragraph 2).

5) **Unpredictability of the art**. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ.409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). Applicants claim a method of inducing an immune response using an M-DNA that encodes **an antigen.** However, applicants have not provided the coding sequence for an antigen nor demonstrated that any such antigen can elicit an immune response. The nature of the DNA is an essential element when considering induction of an immune response. Falo et al teach that the nature of the DNA must be considered- the DNA must be available to the immune system and sustained stimulation is required (paragraph 1-2, page 2 Falo et al). Design of a DAN vaccine in the case of eliciting an immune response against HIV has taught many lessons that can be applied to any antigen. Aidsmap teaches that to elicit an immune response, considerable amounts of DNA are needed to induce the response and in many cases, injecting this amount of DNA is impractical (Aidsmap, paragraph 3). 2) Design of the genes to be introduced requires a safety consideration that makes defining the antigen important. 3) Delivery of the DNA into the skin has not elicited an immune response in macque studies. However, injection into muscle is avoided to avoid integration of the DNA into the cell. 4) The high mutation rate of HIV has allowed it to evade several

vaccines once found to be successful (see Aidsmap, preventing hiv). As such, it is not clear that any antigen encoded by DNA can induce an immune response.

The lack of guidance on methods of eliciting an immune response compounded by the lack of disclosure of well-defined antigenic determinants to be used or direct guidance directed towards the identification of antigenic determinants makes use of the method for eliciting an immune response highly unpredictable. Given the disclosure, it would require undue experimentation to identify the antigenic determinant that would actually provide an immune response that is protective and therapeutic in nature. Therefore, the unpredictability of eliciting an immune response by **an antigen**, the unpredictability of the invention is high.

6) **Summary**. The invention recites a method for the eliciting an immune response in animals and humans by administration of metal containing nucleic acids encoding an antigen. In view of unpredictability of the art to which the invention pertains and the lack of established protocols and the inability to predict what antigenic determinant will elicit a response: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue, unpredictable experimentation in order to practice the claimed invention.

***Response to Argument***

Applicants argue that as amended the claims are enabled. Applicants argue that an antibody response is evidence that components of acquired immunity are activated by the present

invention. Specifically, applicants argue that by showing the antibodies are produced in response to a M-DNA encoded antigen that includes cellular and soluble components of the immune system, an antigen specific immune response has been demonstrated.

Applicants' arguments filed 6/2/05 have been fully considered but they are not persuasive. Applicants have recited a method for eliciting an immune response to an antigen encoded by M-DNA. By immune response, applicants encompass a broad range of responses that are not simply represented by production of an antibody to an antigen. For reasons detailed above, it would require undue experimentation to identify the antigenic determinant that would actually provide an immune response that is protective and therapeutic in nature. Therefore, the unpredictability of eliciting an immune response by **an antigen**, the unpredictability of the invention is high.

***Conclusion***

Claims 1, 6-14 and 18-22 are rejected.

Claims 4 and 17 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

August 19, 2005

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER